Detailed Action

Applicant's response to restriction requirement of 01/10/2008 has been entered.

Claim status. Claims 1-32, 37-42, 44, 46-51 are currently pending as stated by Applicant at page 8, line 1 of Applicant's remarks filed on 04-03-2008. However, claim 46 is not accounted for in the claim listing filed on 04-03-2008. It is noted that the status of every claim must be indicated after its claim number by using one of the following identifiers in a parenthetical expression: (Original), (Currently amended), (Canceled), (Withdrawn), (Previously presented), (New), and (Not entered). Claim 46 of applicant's amendment filed on 01-09-2006, drawn to a method of screening for an RNA sequence, was included in Group V of the restriction requirements filed on 04-03-2008. Applicant has elected **with traverse** Group II. Accordingly, for the purpose of a compact prosecution, claim 46 is considered as a withdrawn claim.

After a telephonic interview with Applicants' attorney of record, Maurice Balla, on 12 June 2008, the examiner was notified that claim 46 was inadvertently not included in the claim listing filed on 04-03-2008 and failed to be identified as a withdrawn claim. Claim 46 will be included and identified as a withdrawn claim by Applicant in the next submitted claim listing.

Applicants' election of Group II in Applicant's reply filed on 04-03-2008, drawn to an *in vitro* method of inducing a totipotent or pluripotent stem cell to differentiate into an adult specialized cell after providing isolated RNA, i.e., claims 1, 3-9, 15-32, 44, 47 and 48, is acknowledged. Election of the following species is acknowledged: the differentiation of a stem cell to an adult specialized cell as recited in claim 6, isolated RNA that is extractable from an individual who shows immunity or resistance to a disease or condition as recited in claim 17, and adult animal stem cells as recited in claims 23, 24 and 47. Upon further consideration, the

examiner has decided to withdraw the restriction requirements among the following species: (i) Adult animal stem cells: bone marrow stromal cells, hematopoietic stem cells or neuronal stem cells or a corresponding derived stem cell line, and (ii) embryonic stem cells or a stem cell line derived from such cells as the genus of stem cells, as recited in claims 23, 24 and 47 because prior art consideration and/or examination of arts relevant to the claimed species as a whole would not be unduly burdensome. Therefore, claims 2, 10-14, 37-42, 46 and 49-51 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention and claims 7-9, 15, 16 and 18 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected species, there being no allowable generic or linking claim.

Response to arguments

Applicant's Arguments of 01/10/2008 in view of the official restriction/ election requirements have been respectfully reconsidered and are found to be persuasive.

At page 9 of Applicant's remarks, Applicant argues that the examiner has not carried the burden of providing any reasons and/or examples to support any conclusion that Groups I-II lack unity of invention. Furthermore, Applicant brings the examiner's attention to the European Patent Office (EPO) because Applicant indicates that the EPO has "considered the inventions of Groups I and II to have "unity of invention" under PCT and EPO provisions. In view of the U. S. Patent and Trademark Office and Congress desire for patent harmonization, applicants encourage the examiner to reconsider the proposed restriction at least as applied to Groups I and II. Therefore applicants would like to suggest that at least Groups I and II should be pursued in a single invention and rejoinder of these groups is requested. Nevertheless, in accordance with 37 CFR §

1.143, applicants hereby provisionally elect Group II for prosecution on the merits". Such is not persuasive.

The expression "special technical features" is defined in PCT Rule 13.2 as meaning those technical features that define a contribution which each of the inventions, considered as a whole, makes over the prior art. The determination is made on the contents of the claims as interpreted in light of the description and drawings (if any). In the instant case , the disclosure of the specification as filed clearly teaches methods for in *vitro* and *in vivo* differentiation of stem cells into specialized cells after providing isolated RNA. For example, at page 24, lines 25-30, page 38, lines 35-36, bridging to page 39, lines 1-36. The cited examples disclose unique technical features in relation to *in vitro* and *in vivo* method, for example, *in vivo* differentiation of stem cells into specialized cells after providing isolated RNA require administration of cells to treat an individual and further considerations of rejection of allogeneic or xenogeneic cells with respect to said individual. Thus the inventions are materially different processes comprising distinct process steps, which therefore necessarily induce in *vitro* and *in vivo* differentiation of stem cells into specialized cells by different modes of action or effect, so as to lack unity of invention and form a single general inventive concept. Furthermore, it is noted that no specific argument or evidence is presented by Applicant demonstrating that the Groups are not patentably distinct or obvious variant of each other.

At page 10 of remarks, Applicants acknowledge election of species of isolated RNA that is extractable from an individual who shows immunity or resistance to a disease or condition as recited in claim 17. However, Applicant alleges that "applicants do not believe this source of RNA is particularly relevant to the inventions of Group II above. Alternatively, applicants would

prefer to elect the source or RNA recited in the description at page 16, lines 20-24 (i.e., cells comprising the desired differentiated cell type(s)). Applicants welcome a response from the examiner to this alternative source of RNA". Such is not persuasive.

At the outset, the examiner directs Applicants attention to the fact the there is not recitation in any of the claims filed on 04-03-2008 of an isolated RNA sequence that is extractable from "cells comprising the desired differentiated cell type(s)", as applicant contents. Hence the argument is not persuasive as it argues limitations that are not present in the claims.

Therefore, for these reasons and the reasons set forth in the Office action filed on 01/10/2008, these inventions do not share unity of invention as required under PCT Rule 13 and the restriction/election requirement is still deemed proper and is therefore made FINAL.

Therefore, claims 1, 3-6, 17, 19-32, 44, 47 and 48 are currently being examined to which the following grounds of rejection apply.

Information Disclosure Statement

The listing of references in the specification is not a proper information disclosure statement. 37 CFR 1.98(b) requires a list of all patents, publications, or other information submitted for consideration by the Office, and MPEP § 609.04(a) states, "the list may not be incorporated into the specification but must be submitted in a separate paper." Therefore, unless the examiner on form PTO-892 has cited the references, they have not been considered.

The information disclosure statement filed on October 19, 2006 has been reviewed, and their references have been considered as shown by the Examiner's initials next to each citation on the attached copy.

The information disclosure statement filed on October 19, 2006 fails to comply with 37 C.F.R. § 1.98(a)(2), which requires a legible copy of each U.S. and foreign patent; each publication or that portion which caused it to be listed; and all other information or that portion which caused it to be listed.

The following references were not considered for the reasons described below:

a) Reference 103 is incomplete in the absence of a legible copy.

All other documents in said Information Disclosure statement were considered as noted by the Examiner initials in the copy attached hereto.

Priority

Acknowledgment is made of applicant's claim for foreign priority under 35 U.S.C. 119(a)-(d). The certified copy of the foreign application GB 0316089.2 has been filed on 01-09-2006.

Claim Rejections - 35 USC § 112- Second Paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter, which the applicant regards as his invention.

Claim 47 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite in that it fails to point out what is included or excluded by the claim language.

Claim 47 which depends on claim 23 recites "wherein said adult stem cells". However, claim 23 only refers to "adult animal stem cells or adult stem cell line". Thus there is not a

proper antecedent bases for said "adult stem cells" in claim 23. As such, the metes and bounds of the claims cannot be determined.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1, 3-5, 17, 29, 30, 31 and 44 are rejected under 35 U.S.C. 102(b) as being anticipated by Cezayirli et al., (U.S. Patent Pub. No: 2001/0001066, Date of Publication May 10, 2001, of record).

Cezayirli teaches methods for directing precursor dendritic cells (DCs) to Programmable Antigen Presenting Cells (pAPCs) having the capacity to direct a complete and/or specific immune response to any number of tumor antigen moieties after being "loaded" with either tumor derived RNA or the poly A+ population (p. 2, paragraph [0009]). Furthermore, Cezayirli teaches that the donor host for the pAPCs can the same host receiving the pAPCs as vaccines directed to particular tumors, or any host of the same allotype with the same disease, exhibiting such RNA or poly A+ portion (p. 2, paragraph [0016]; p. 5, paragraph [0038]) (Current **claims 1, 3, 4, 29 and 44**). Cezayirli contemplates immortalization of the pAPC to allow for a suitable continuous source of cells as an allogenic vaccine (p. 3, paragraph [0021]; p. 3, paragraph [0024) (Current **claim 5**). In addition, Cezayirli discloses that tumor cell RNAs can be isolated from biopsy material that has been prepared in paraffin block storage for direct incorporation into the DC. Moreover, Cezayirli discloses that the DCs ingest cells' RNA (p. 4, paragraphs [0027],

[0031]) (Current **claims 30 and 31**). The RNA used to transform DCs can be derived from autologous tumor cell lysates (p.5, paragraph [0038]; p.4, paragraph [0025]) or other individuals tumors (e.g., allogenic pAPCs)(pp.3-4, paragraph [0023]). Though Cezayirli does not explicitly disclose an individual who shows immunity or resistance to conditions, all individuals are resistant to diseases in varying degrees, absent evidence to the contrary. Note that claims 17 and 29 are no limited to methods step but rather limit the RNA structure, e.g., the RNA is extractable (Current **claims 17 and 29**).

Thus by teaching all the claims limitations, Cezayirli anticipates the instant invention.

Claim Rejections - 35 USC § 103

The current claims are examined to the extent that they embrace an *in vitro* method comprising the induction of differentiation of stem cells into an adult specialized cell.

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1, 6, 19-29, 32, 47 and 48 are rejected under 35 USC 103 as being unpatentable over Sanyal et al., (*Proc Natl Acad Sci* U S A. 1966, pp: 743-50, or record), in view of Franks et al., (WO 02/24873, Date of Publication 28 March 2002, of record).

Sanyal teaches that treatment of the definitive streak stage (Hamburger and Hamilton stage 4) of chick embryo with isolated RNA from chick brain and chick liver resulted in

development of neuronal structures and mesenchymal cells in relation to non treated primitive streak (p. 745-746, Table 1). Moreover, Sanyal describes the effects of other sources of isolated RNA e.g., calf brain, liver, kidney and hearth in blastoderm of chick embryo inducing distinct developmental occurrence of neuronal and non-neuronal structures (p. 745, last paragraph). Furthermore, Sanyal discloses that the correlation between RNA tissue source and the specific structures produced suggest the transfer of organ specifity or information by its RNA to the target cells (p. 748, last paragraph).

Worden does not specifically teach providing isolated RNA to stem cells.

However, at the time the invention was made, Franks et al., discloses the generation of a pluripotent cell comprising transferring of hematopoietic donor stem cell nucleus or nuclear transfer from a somatic donor cell into an activated recipient oocyte to generate a cell mass, e.g., teratoma-like cell mass, which is grown *in vitro* in the appropriate conditions for further growth and differentiation to the selected tissue(p. 9, lines 10-24, p. 10, lines 10-16; p. 22, lines 8-31; p. 24, line 5; p. 27, lines 10-18; p.29, lines 10-14). Additionally, Franks et al., teaches that a differentiated cell type can be a neuronal cell (p. 21, lines 4-7; p. 23, lines 25-30; p. 25, lines 19-23) (Current **claims 1, 6, 19-22, 24-26 and 48**). Furthermore, Franks et al., discloses that the cell nucleolus of the recipient oocyte can remove before or after the transfer (p. 23, lines 25-30) (Current **claim 27**). The donor cells may be derived from the intended recipient host (p. 22, lines 17-30; p. 26, lines 16-20 p. 28, lines 2-3) (Current **claim 28**) or may be allogenic to the patient requiring treatment (p. 26, lines 21-25) (Current **claim 29**). Moreover, the donor cells may be selected form hematopoietic stem cell, or any type of somatic cell including fibroblasts (p. 12, lines 5-18) (Current claims **23, 32 and 47**).

Therefore, in view of the of the effects induced by providing isolated RNA to the blastoderm of chick embryos resulting in self-differentiation and the capacity of chick blastoderm to develop into neuronal tissue and non-neuronal tissue depending on the source of isolated RNA as taught by Sanyal, it would have been *prima facie* obvious for one of ordinary skill in the art to replace the chick blastodermic layer of cells with stem cells to study the effect of exogenous RNA on stem cell differentiation, particularly because both embryonic cell lines e.g., chick blastoderm and stem cells differentiate into neuronal and non neuronal tissues. Furthermore, Franks clearly exemplifies differentiation of genetically engineered stem cells into a wide range of differentiated cell/tissue types. The manipulation of previously identified RNA fragments and cell transformation systems is within the ordinary level of skill in the art of molecular biology. One of ordinary skill in the art would have had a reasonable expectation of success in generating a method comprising providing isolated RNA to differentiate stem cells into a desire adult cell phenotype by substituting the blastoderm of the chick embryo taught by Sanyal with the pluripotent "teratoma-like" cell masses taught by Franks to achieve the predictable result of inducing distinct developmental occurrence of neuronal and non-neuronal structures, given the results of both Sanyal and Franks demonstrating the success of the methodology and materials detailed in each of the disclosures.

Provisional Rejection, Obviousness Type Double Patenting-

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the

examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1, 3-6, 17, 19-31, 44, 47 and 48 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1, 3-11 and 16-19 of copending Application No. 11/814271. Although the conflicting claims are not identical, they are not patentably distinct from each other because they are obvious variants.

The claims of copending Application No. 11/814271, are drawn to a method of inducing genotypic modification in a cell comprising providing isolated RNA comprising RNA extractable from source tissue to the cell under conditions whereby the desired induction of genotypic modification is achieved, wherein the RNA is isolated polyA positive RNA in substantially pure form.

The instant claims are drawn to method of altering a property of a cell towards a property of one or more desired cell types comprising providing isolated RNA comprising a RNA sequence extractable from cells comprising said desired cell type(s) to a population of cells under conditions whereby the alteration of the cell property is achieved.

The instant claims differ from claims 11, 3-11 and 16-19 of copending Application No. 11/814271 by no requiring the isolated RNA to be polyA positive RNA. As he instant claims embrace a genus of isolated RNAs including messenger RNA (mRNA), ribosomal RNA (rRNA), transfer RNA (tRNA), heterogeneous nuclear RNA (hnRNA), small nuclear RNA (snRNA), small cytoplasmic RNA (scRNA), small nucleolar RNA (snoRNA), transcription-related RNAs, splicing-related RNAs, signal recognition particle RNA, polyA positive RNA and others, claims 1, 3-6, 17, 19-31, 44, 47 and 48 of the instant invention broadly embrace claims 11, 3-11 and 16-19 of copending Application No. 11/814271. Therefore, claims 11, 3-11 and 16-19 are species of the instantly claimed invention and will anticipate the genus claims.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Conclusion

Claims 1, 3-6, 17, 19-32, 44, 47 and 48 are rejected.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Maria Leavitt whose telephone number is 571-272-1085. The examiner can normally be reached on M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Joseph Woitach, Ph.D can be reached on (571) 272-0739. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Group Art Unit 1633; Central Fax No. (571) 273-8300. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

Patent applicants with problems or questions regarding electronic images that can be viewed in the Patent Application Information Retrieval system (PAIR) can now contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance. Representatives are available to answer your questions daily from 6 am to midnight (EST). The toll free number is (866) 217-9197. When calling please have your application serial or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. The Patent Electronic Business Center will notify applicants of the resolution of the problem within 5-7 business days. Applicants can also check PAIR to confirm that the problem has been corrected. The USPTO's Patent Electronic Business Center is a complete service center supporting all patent business on the Internet. The USPTO's PAIR system provides Internet-based access to patent application status and history information. It also enables applicants to view the scanned images of their own application file folder(s) as well as general patent information available to the public.

/Maria Leavitt/

Maria Leavitt, PhD
Examiner, Art Unit 1633